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Is T-Wave Alternans As Good or Better than Programmed Ventricular Stimulation?

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Improved prognostic indices are needed to identify risk for sudden cardiac arrest (SCA) from ventricular arrhythmias (VT/VF). Current methods rely upon reduced left ventricular ejection fraction (LVEF) and symptomatic heart failure, but in this way assign high-risk to many patients who never experience events (1). Although indices of ventricular stretch, such as elevated B-type natriuretic peptide (2), of enhanced sympathetic activation (3), or of ventricular scar (4) show promise, 'electrical' indices are natural candidates. Inducing sustained VT/VF at programmed ventricular stimulation ('positive' PVS) adds prognostically to reduced LVEF (5), and provided 1 and 2-year negative predictive values (NPV) of ≈ 93 % and 88 % for arrhythmic events in the Multicenter Unsustained Tachycardia Trial (MUSTT) (6) (table). However, debate on whether the 7–12 % risk of arrhythmias at 1–2 years in a patient with negative PVS was low enough to withhold implantable cardioverter-defibrillator (ICD) therapy has motivated the search for alternative indices. This list includes heart rate variability (7), signal-averaged ECG (8) and widened QRS duration (9,10), but much recent interest has focused on T-wave alternans.

T-wave alternans (TWA) is defined as alternate-beat fluctuations in the ECG T-wave, and reflects repolarization dispersion that is mechanistically linked with ventricular arrhythmias (11–13). Clinically, TWA is attractive because it is non-invasive and has a high NPV for arrhythmic events, so that patients who test negative for TWA may not require ICDs (14) (table). This NPV must be maintained as TWA is more widely applied in risk stratification guidelines (15). This is especially relevant given the recently presented negative result of the TWA substudy of the Sudden Cardiac Death in Heart Failure Trial (SCD-HefT) (16), in which TWA failed to predict SCA, sustained VT/VF or appropriate ICD therapy (hazard ratio 1.28, p=0.46) in 490 patients with class II/III NYHA heart failure and LVEF≤ 35%.

The Current Study

It is in this context that the study by Morin et al. (17) in this issue of *Heart Rhythm* is particularly timely. The authors report a single-center experience of 386 MUSTT-type patients with coronary disease, LVEF ≈ 29±8 % and non-sustained VT undergoing PVS and TWA testing for the primary end-point of arrhythmia-free survival (appropriate ICD therapy, documented VT/VF or all-cause mortality) at 2 years. TWA identified patients reaching this end-point, with

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a predictive value equivalent to PVS. However, neither index was valuable in patients with ECG QRS widening (defined as QRS duration > 120 ms). These conclusions are important and warrant further discussion.

First, Morin et al. (17) report a 2-year NPV for arrhythmia-free survival of 84% for TWA and 86 % for PVS in patients with narrow QRS (lower in those with QRS widening). Although surprising, this near-equivalence of PVS and TWA was recently presented in the Alternans Before Cardioverter Defibrillator (ABCD) study (18), of 566 MUSTT-type patients with LVEF 28±7 % (table). In both studies, the NPV of TWA was similar to those of PVS in MUSTT (table), and in ABCD the 1-year NPV improved to 98 % if TWA and PVS were combined (18,19). This range of NPV is actually similar to earlier studies. The 'TWA labeling study' (20) included a 'ventricular-arrhythmia subgroup' of 215 patients (LVEF 39±18%, 55% with coronary disease, 27 % with prior sustained VT/VF), in whom PVS and TWA gave NPV for arrhythmic events of 92 % and 97 % at 14 months, respectively (table). The TWA in CHF study also reported a very high NPV (21) (table) in patients with ischemic or non-ischemic cardiomyopathy. It is therefore curious that the SCD-HefT substudy of similar patients failed to show predictive value for TWA (16). Final publication of those data may reveal if technical factors in data acquisition or specific clinical characteristics of the patients studied are implicated.

Second, Morin et al. (17) found that neither TWA nor PVS predicted arrhythmia-free survival in patients with QRS widening, compared to patients with narrow QRS complexes (hazard ratios for abnormal tests: 1.04 vs 1.64, and 0.94 vs 2.28, respectively). For TWA, NPV was 84 % in patients with narrow QRS complexes but only 68% in those with wide QRS complexes. A similar relationship was found for PVS. Analyzing results by quartile, TWA 'lost' predictive value for QRS duration > 92 ms. Although provocative, this conclusion hinges upon outcome in the small cohort with bundle branch block who tested TWA normal (n=25). Nevertheless, it supports an important study by Rashba et al. (22), in which neither TWA nor PVS predicted arrhythmia-free survival in the presence of QRS widening, in 108 patients with ischemic cardiomyopathy studied for primary and secondary prevention. In both studies, TWA was likely less effective because patients with QRS widening suffered high event rates, echoed by some (9) but not all (10) studies of patients at risk for SCA. Although it is possible that QRS widening *per se* weakens TWA analysis, TWA remains effective when measured during ventricular pacing (23–27). The TWA in CHF and Ohio/Michigan studies (14,21) reported higher event rates in patients with QRS widening, but neither reported NPV of TWA based on QRS width. This issue is important for the bedside application of TWA to individual patients, and may be clarified by the formal subgroup analysis of the ABCD and SCD-HefT TWA substudy or other ongoing trials of TWA (13).

It is important to consider whether the results by Morin et al. (17) may be influenced by confounding factors. However, their patients had a similar 2-year event rate to that reported in MUSTT (5), and comparable age, LVEF, incidence of QRS widening (≈30%) and 2-year event rates to those in recent TWA trials (14,21). Thus, differences in the incidence of non-sustained VT (required by Morin et al. (17), unreported in prior TWA trials (14,21)), syncope (more common in the Ohio/Michigan study (14)), symptomatic heart failure and usage of angiotensin converting-enzyme or angiotensin receptor blockers are of unclear significance. A potential source of error is in the assignment of events. Since patients with wide QRS were more likely to receive ICDs, this may have led to 'over-reporting' of nonfatal arrhythmias compared to patients with narrow QRS. In addition, Morin et al. (17) continued beta-blockers during TWA testing, that may theoretically attenuate TWA and impair its NPV (13). On the other hand, recent TWA trials reported high NPV for TWA either with (21) or without (14) continued beta-blockade during testing. Finally, exercise-TWA may be superior to TWA from atrial pacing

(as used by Morin et al. (17)), although this may influence the NPV less than other parameters (28).

Conclusions

The final word on whether TWA has a better predictive value for arrhythmic events in patients with ischemic cardiomyopathy than PVS awaits publication of the ABCD study. Nevertheless, existing data in large numbers of patients show that non-invasive exercise-TWA is at least as effective as invasive PVS. The results of Morin et al. (17), that TWA and PVS are more effective in patients with narrow QRS durations, support arguments for a tailored rather than off-the-peg approach to defining SCA risk (10). Since an individual's arrhythmic substrate likely evolves over time (1), TWA is a therefore a potentially useful tool for annual non-invasive risk assessment – ICD therapy could be withheld if TWA remains negative. Studies are needed to address that hypothesis. Just as importantly, an open debate is required to determine the negative predictive value that is sufficiently high to withhold ICD therapy if a patient tests negative with any combination of prognostic indices.

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Table

Negative Predictive Values for Endpoints That Include Arrhythmias

Study and Reference		Sample Size	LVEF	Test	Endpoint	NPV	
						1Y	2Y
MUSTT	(6)	1750	29	PVS	SCA/VT/VF	≈93	88
Morin et al. *	(17)	386	29±8	PVS	Death/VT/VF	≈95	86
				TWA		≈90	84
ABCD	(18)	566	28±7	PVS	SCA/VT/VF	95	–
				TWA		95	–
TWA Labeling Study †	(20)	215	39±18	PVS	Death/VT/VF	≈92	–
				TWA		≈97	–
TWA in SCD-HefT †‡	(16)	490	25	TWA	SCA/VT/VF	90	88
TWA Meta-Analysis	(29)	–	mixed	TWA	SCA/VT/VF	–	≈97
TWA in CHF †	(21)	549	25±6	TWA	Death/VT/VF	99	97
Ohio/Michigan	(14)	768	27±5	TWA	Death/VT/VF	–	≈85
					SCA/VT/VF	–	≈95

Key:

*NPV for patients with narrow QRS only;

†study included approximately equal numbers of patients with ischemic and non-ischemic cardiomyopathy. NPV – negative predictive value; SCA – sudden cardiac arrest; VT/VF – sustained ventricular arrhythmias;

‡TWA was non-predictive (similar event rates for normal and abnormal TWA).